Oncogene 1998 Apr 2;16(13):1723-30

Expression of mouse telomerase reverse transcriptase during development, differentiation and proliferation.

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We have identified the mouse telomerase reverse transcriptase component (mTERT) and demonstrate both substantial sequence homology to the human ortholog (hTERT), and the presence of reverse transcriptase and telomerase specific motifs. Furthermore, we show functional interchangeability with hTERT in in vitro telomerase reconstitution experiments, as mTERT produces strong telomerase activity in combination with the human telomerase RNA component hTR. The mouse TERT is widely expressed at low levels in adult tissues, with greatest abundance during embryogenesis and in adult thymus and intestine. The mTERT component mRNA levels were regulated during both differentiation and proliferation, while mTR levels remained constant throughout both processes. Comparison of mTERT and mTR levels to telomerase activity indicates that mTERT expression is more tightly linked to the regulation of telomerase activity during these processes than is mTR. In contrast to the situation in human cell cultures, mTERT transcript levels are present at readily detectable levels in primary cultured cells and are not upregulated following crisis. The widespread expression of mTERT in primary cells and mouse tissues could explain the increased frequency of spontaneous immortalization of mouse cells in culture and tumorigenesis in vivo.

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Mouse models for the study of telomerase.

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The ends of chromosomes, or telomeres, consist of short repeated sequences that are synthesized by a ribonucleoprotein-DNA polymerase called telomerase. The RNA component of telomerase is essential for enzyme activity. The maintenance of telomere length by telomerase has been proposed to be essential for cellular viability and to play an important role in cellular senescence and immortalization. We are interested in using the mouse as a model system for the study of telomerase. We studied telomerase activity and expression of the mouse telomerase RNA component (mTR) in two different transgenic mouse models of multistage tumorigenesis: models of islet cell carcinoma and squamous cell carcinoma. In both tumour models, telomerase activity was detected only in late-stage tumours, whereas the telomerase RNA was present at higher than normal levels in pre-neoplastic stages and increased further in late-stage tumours. However, the RNA levels did not parallel the amounts of telomerase activity detected, suggesting that regulation of telomerase activity does not correlate with the regulation of its RNA component. These results establish a direct correlation between progression to late-stage tumours and induction of telomerase activity, and suggest that the initial upregulation of telomerase RNA is an early event. To address the role of telomerase during normal mouse development and tumour formation, we have constructed a knockout mouse for the mouse telomerase RNA, mTR-/-. These mice and the cell lines derived from them are telomerase deficient.

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Hum Mol Genet 1997 Nov;6(12):1999-2004

Mammalian telomerase: catalytic subunit and knockout mice.

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For the second time this year random cDNA sequencing, in combination with data from unicellular eukaryotes, has made a significant contribution to the analysis of human telomerase. Two groups have reported mammalian homologues of the Tetrahymena p80 telomerase-associated protein, in both cases the key breakthrough being mammalian cDNA clones with database matches to Tetrahymena p80. This has now been joined by the sequence of a candidate for the human telomerase catalytic subunit. The discovery that its message abundance closely follows telomerase activity could make a major impact on the utility of telomerase as a diagnostic marker for human malignancy. In addition, Blasco et al . report the phenotype of a transgenic mouse deleted for the mTR gene, which encodes the essential RNA component of telomerase. Interestingly tumour formation is unaffected in these mice, strengthening the argument that telomerase expression in mouse tumourigenesis is an innocent bystander rather than a necessary event. However, fundamental differences between the genomic organisation of mouse and human telomeres mean that the mouse is not a straightforward model to critically test the role of telomere loss and telomerase in human malignancy.

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Nature 1998 Apr 9;392(6676):569-74

Essential role of mouse telomerase in highly proliferative organs.

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We have investigated the role of the enzyme telomerase in highly proliferative organs in successive generations of mice lacking telomerase RNA. Late-generation animals exhibited defective spermatogenesis, with increased programmed cell death (apoptosis) and decreased proliferation in the testis. The proliferative capacity of haematopoietic cells in the bone marrow and spleen was also compromised. These progressively adverse effects coincided with substantial erosion of telomeres (the termini of eukaryotic chromosomes) and fusion and loss of chromosomes. These findings indicate an essential role for telomerase, and hence telomeres, in the maintenance of genomic integrity and in the long-term viability of high-renewal organ systems.

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